ORGANIC CHEMISTRY
FRONTIERS

RESEARCH ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Org. Chem. Front.*, 2015, **2**, 476

Enantioselective synthesis of 4,5,6,7-tetrahydroindoles *via* olefin cross-metathesis/intramolecular Friedel–Crafts alkylation reaction of pyrroles†

Jun-Wei Zhang,[a,b] Xiao-Wei Liu,[a] Qing Gu,[a] Xiao-Xin Shi[b] and Shu-Li You*[a,b]

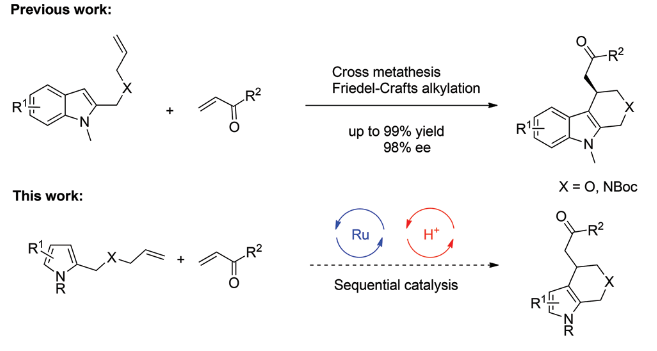
Received 27th January 2015,
Accepted 21st February 2015

DOI: 10.1039/c5qo00034c

rsc.li/frontiers-organic

A sequential catalysis involving olefin cross-metathesis/asymmetric intramolecular Friedel–Crafts alkylation of pyrrole derivatives has been developed. A variety of enantioenriched 4,5,6,7-tetrahydroindoles were obtained in good yields and enantioselectivity by combining a Zhan-1B catalyst with a chiral phosphoric acid.

Over the past several years, sequential catalysis consisting of a transition-metal catalyst and a chiral phosphoric acid (CPA) has been one of the most effective synthetic approaches for the construction of complex molecules with diverse functional groups in a single operation.[1–3] In addition, this system also features the utilization of readily available starting materials, minimization of wastes and reduction of labor. Most notably, it could achieve novel and unprecedented transformations due to the synergistic effects within two catalytic processes, providing important chiral scaffolds which could not be obtained by employing either single catalyst alone. Therefore sequential catalysis has now become an intense research area in organic synthesis. In 2009, our group demonstrated a sequential catalysis involving Ru-catalyzed olefin cross-metathesis followed by a subsequent Brønsted acid catalyzed intramolecular Friedel–Crafts alkylation of indoles, providing a variety of enantioenriched and biologically active polycyclic indoles (Scheme 1, top).[4] To the best of our knowledge, however, there is no example of a sequential reaction involving cross-metathesis and Friedel–Crafts alkylation based on pyrrole scaffold despite its frequent occurrence in biologically active natural products and pharmaceuticals.[5] Compared with indoles, fewer asymmetric Friedel–Crafts alkylation reactions of pyrroles[6,7] were reported, likely due to the increased challenges on regio- and enantioselective control. With our continuing interest in sequential catalysis,[4,8] we envisioned that cross-metathesis



Scheme 1 Cross-metathesis and asymmetric Friedel–Crafts alkylation of indoles and pyrroles.

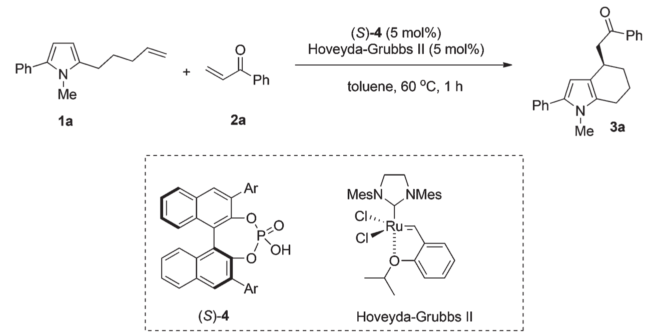
and asymmetric Friedel–Crafts alkylation of pyrroles might be achieved by fine tune of the substrates and catalysts (Scheme 1, below). Herein we report such a sequential catalysis involving pyrrole substrates for the synthesis of enantioenriched tetrahydroindoles.[9]

We began our studies by examining chiral phosphoric acids with different substituents in the sequential reaction between pyrrole olefin **1a** and phenyl vinyl ketone **2a**. The reaction of **1a** and 1.5 equivalents of phenyl enone **2a** in the presence of 5 mol% chiral phosphoric acid (*S*)-**4** and 5 mol% Hoveyda–Grubbs II in toluene at 60 °C all proceeded to completion within 1 hour to give the desired product in good yields (56–71%) and moderate to good enantioselectivity (18–62% ee). As summarized in Table 1, the substituent of the catalyst had a great influence on the enantioselectivity of the reaction. Chiral phosphoric acids **4c** bearing 1-naphthyl groups and **4e** bearing 4-biphenyl groups proved to be the most efficient catalysts in terms of reactivity and enantioselectivity, affording **3a**

[a]State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China
[b]School of Pharmacy, East China University of Science and Technology, 130 Mei-Long Road, Shanghai 200237, China. E-mail: slyou@sioc.ac.cn

† Electronic supplementary information (ESI) available. CCDC 1045810. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5qo00034c

Table 1 Screening of chiral phosphoric acids[a]



Entry	4, Ar	Yield[b] (%)	ee[c] (%)
1	**4a**, 2,4,6-(^{i}Pr)$_3$-C_6H_2	61	18
2	**4b**, $SiPh_3$	65	20
3	**4c, 1-naphthyl**	**56**	**62**
4	**4d**, 2-naphthyl	64	19
5	**4e**, 4-biphenyl	71	60
6	**4f**, 4-NO_2-C_6H_4	67	44
7	**4g**, 4-[3,5-$(CF_3)_2$-C_6H_3]-C_6H_4	66	50
8	**4h**, 9-anthryl	60	52
9	**4i**, 9-phenanthryl	59	55
10	**4j**, 3,5-$(CF_3)_2$-C_6H_3	61	29
11	**4k**, 2-isopropoxy-1-naphthyl	66	54

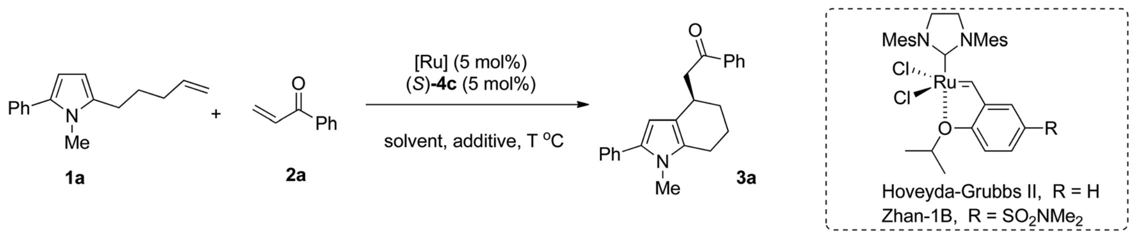
[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), Hoveyda–Grubbs II (5 mol%) and (*S*)-**4** (5 mol%) in toluene (2 mL) at 60 °C. [b] Isolated yield. [c] Determined by HPLC analysis.

in 56% yield, 62% ee and 71% yield, 60% ee respectively (Table 1, entries 3 and 5).

Encouraged by these results, other reaction parameters such as reaction temperature, ruthenium catalysts and solvents were further investigated with (*S*)-**4c** as the optimal Brønsted acid. The results are summarized in Table 2. At a lower temperature, the reaction delivered the corresponding product with an increased ee value albeit slightly decreased yield (Table 2, entries 1–4). For example, when the reaction was performed at 40 °C, the ee value of the product could be increased to 72% (Table 2, entry 2). Notably, Zhan-1B could also provide product **3a** in 70% ee with a slightly higher yield (54% yield) (Table 2, entry 5). Given its cheapness, Zhan-1B was used for further optimization of the reaction conditions. Among the molecular sieves with different sizes, the addition of 3 Å MS gave better results (Table 2, entry 6, 60% yield, 72% ee). Other solvents such as *o*-xylene, CH_2Cl_2, THF and ether all led to the formation of **3a** in comparable yields but with decreased enantioselectivity (Table 2, entries 9–12, 66–72% yields and 32–54% ee). To our great delight, the amount of enone **2a** could be further reduced to 1.2 equivalents without the erosion of yield and enantioselectivity (Table 2, entry 13, 60% yield, 72% ee). Thus the optimized conditions were obtained as the following: 5 mol% of (*S*)-**4c**, 5 mol% of Zhan-1B, 1.2 equivalents of enone **2**, 3 Å MS as an additive in toluene at 40 °C.

Under the above mentioned optimized reaction conditions, we then examined the substrate scope of this reaction. The results are summarized in Table 3. Besides phenyl enone,

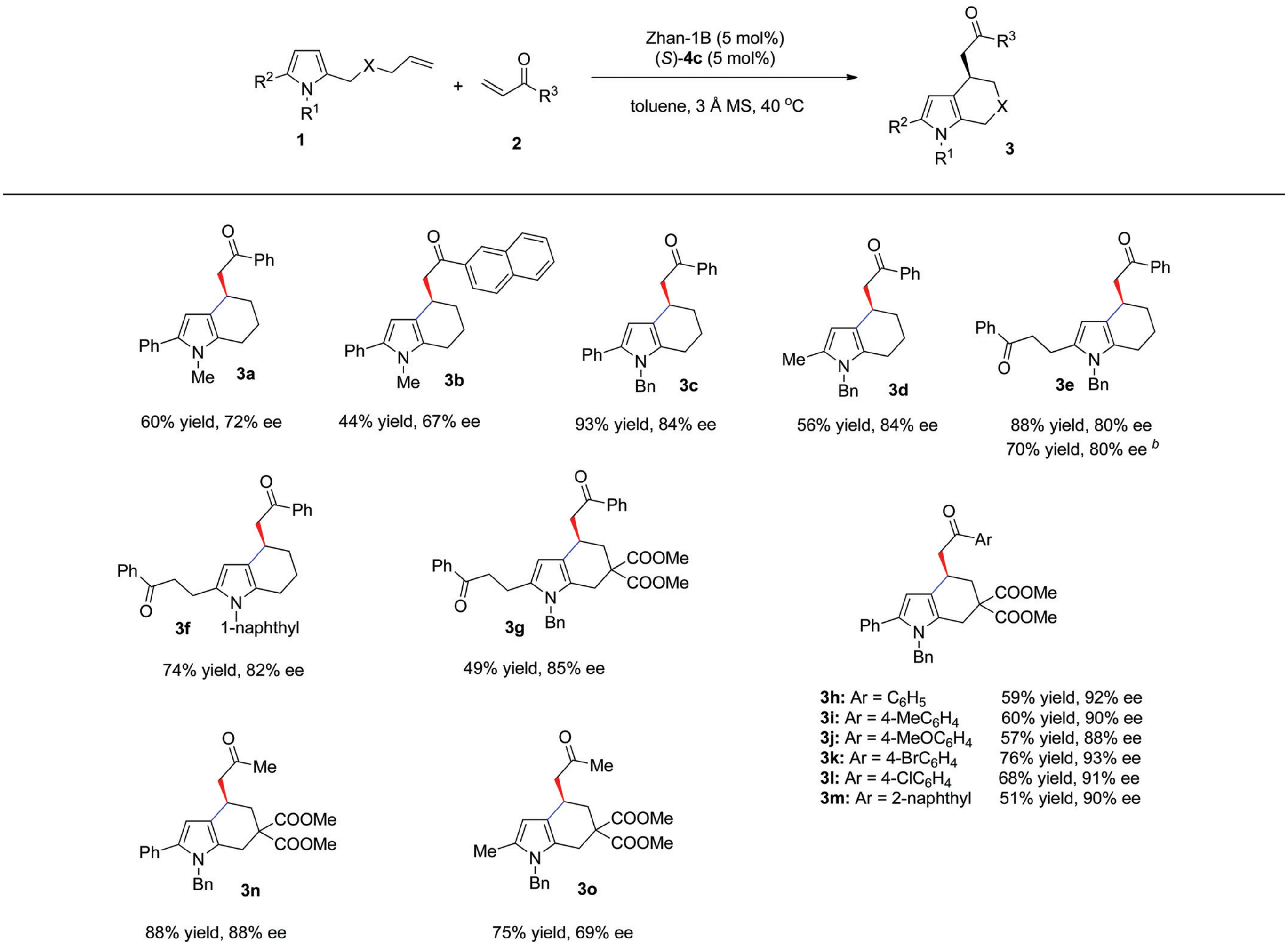
Table 2 Optimization of the reaction conditions for the sequential reaction[a]



Entry	[Ru]	Additive	Solvent	Temp (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	Hoveyda–Grubbs II	None	Toluene	60	1	56	62
2	Hoveyda–Grubbs II	None	Toluene	40	1	50	72
3	Hoveyda–Grubbs II	None	Toluene	rt	10	52	70
4	Hoveyda–Grubbs II	None	Toluene	0	10	25	68
5	Zhan-1B	None	Toluene	40	1	54	70
6	Zhan-1B	3 Å MS	Toluene	40	1	60	72
7	Zhan-1B	4 Å MS	Toluene	40	1	58	70
8	Zhan-1B	5 Å MS	Toluene	40	1	43	72
9	Zhan-1B	3 Å MS	CH_2Cl_2	40	1.5	66	50
10	Zhan-1B	3 Å MS	*o*-Xylene	40	1	67	44
11	Zhan-1B	3 Å MS	Et_2O	40	3	66	54
12	Zhan-1B	3 Å MS	THF	40	1	72	32
13[d]	**Zhan-1B**	**3 Å MS**	**Toluene**	**40**	**1**	**60**	**72**

[a] Reaction conditions: **1a** (0.20 mmol), **2a** (0.30 mmol), Ru catalyst (5 mol%), (*S*)-**4c** (5 mol%) and MS (100 mg) in solvent (2 mL). [b] Isolated yield. [c] Determined by HPLC analysis. [d] 0.24 mmol of **2a** was used.

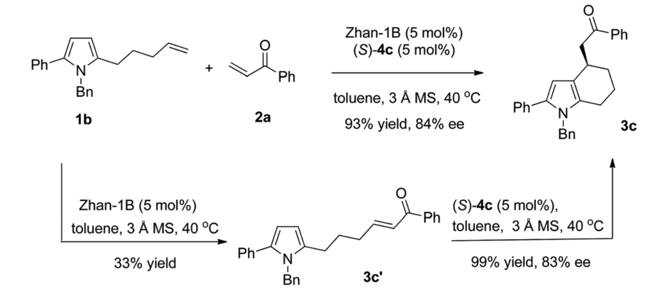
Table 3 Substrate scope of the sequential reaction[a]



[a] Reaction conditions: **1** (0.20 mmol), **2** (0.24 mmol), Zhan-1B (5 mol%), (*S*)-**4c** (5 mol%) and 3 Å MS (100 mg) in toluene (2 mL) at 40 °C. [b] Reaction of **1c** (R^1 = Bn, R^2 = H, X = CH_2) and **2a** (R^3 = Ph, 0.4 mmol, 2.0 equiv.).

2-naphthyl enone (**2b**) was also a suitable substrate, giving **3b** in 44% yield and 67% ee. With *N*-Bn protected pyrrole olefin (**2c**) as a substrate, both enantioselectivity and yield were significantly increased (Table 3, **3c**, 93% yield, 84% ee). When the phenyl group at the C5 position of pyrrole was replaced by methyl or benzoylethyl, the sequential reaction also occurred smoothly, affording the tetrahydroindole products in good yields and ee (**3d**: 56% yield, 84% ee; **3e**: 88% yield, 80% ee). Interestingly, when pyrrole olefin without a substituent at the C5 position (**1c**, R^1 = Bn, R^2 = H, X = CH_2) was used, with 2.0 equivalents of enone **2a**, the same product (**3e**) could be obtained with identical ee and slightly decreased yield (70% yield, 80% ee) through an intermolecular Friedel–Crafts, cross-metathesis and intramolecular Friedel–Crafts reaction cascade. In addition, *N*-1-naphthyl protected pyrrole gave comparable results (**3f**: 74% yield, 82% ee). The carbon-tethered pyrrole olefin was also compatible under the optimal reaction conditions, affording **3g** in 49% yield and 85% ee. Other substituted pyrrole olefins bearing an electron-donating or electron-withdrawing group were also well tolerated and led to their corresponding products (**3h–m**) in good yields (51–76%) and excellent enantioselectivity (88–93% ee). It is worth noting that aliphatic enone such as methyl vinyl ketone was also a suitable substrate (**3n**, 88% yield, 88% ee; **3o**, 75% yield, 69% ee).

The advantage of a sequential reaction was demonstrated by comparison with the synthesis of tetrahydroindole **3c** in a stepwise approach. The olefin cross-metathesis reaction of pyrrole olefin **1b** with phenyl vinyl ketone **2a** catalyzed by Zhan-1B gave intermediate **3c′** in 33% yield together with racemic **3c** in 52% yield due to its easy cyclization during purification. Tetrahydroindole **3c** was then obtained through (*S*)-**4c** catalyzed intramolecular Friedel–Crafts alkylation in 33% yield and 83% ee over two steps (Scheme 2). The sequential reaction avoids troublesome separation processes and increases the yield of the synthesis dramatically.



Scheme 2 Stepwise reactions *vs.* sequential reaction.

In summary, we have developed Zhan-1B in combination with a chiral phosphoric acid catalyzed olefin cross-metathesis/asymmetric intramolecular Friedel–Crafts alkylation of pyrrole derivatives. This sequential catalysis provides a concise and efficient approach to construct chiral 4,5,6,7-tetrahydroindoles in good yields and enantioselectivity from readily available starting materials. Development of more sequential reactions based on dual catalysis is currently ongoing in our laboratory.

Acknowledgements

We thank the National Basic Research Program of China (973 Program 2015CB856600) and the National Natural Science Foundation of China (21272253, 21332009, 21361140373, 21421091) for generous financial support.

Notes and references

1 For reviews on the combination of a transition metal and chiral phosphoric acid catalysis: (*a*) Z. Shao and H. Zhang, *Chem. Soc. Rev.*, 2009, **38**, 2745; (*b*) M. Rueping, R. M. Koenigs and I. Atodiresei, *Chem. – Eur. J.*, 2010, **16**, 9350; (*c*) J. Zhou, *Chem. – Asian J.*, 2010, **5**, 422; (*d*) C. Zhong and X. Shi, *Eur. J. Org. Chem.*, 2010, 2999; (*e*) Z. Du and Z. Shao, *Chem. Soc. Rev.*, 2013, **42**, 1337; (*f*) X. Wu, M. Li and L. Gong, *Acta Chim. Sin.*, 2013, **71**, 1091; (*g*) F. Lv, S. Liu and W. Hu, *Asian J. Org. Chem.*, 2013, **2**, 824; (*h*) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.*, 2014, **114**, 9047; (*i*) D.-F. Chen, Z.-Y. Han, X.-L. Zhou and L.-Z. Gong, *Acc. Chem. Res.*, 2014, **47**, 2365; (*j*) Z.-P. Yang, W. Zhang and S.-L. You, *J. Org. Chem.*, 2014, **79**, 7785.

2 Selected examples of the combination of a transition metal and chiral phosphoric acid catalysis: (*a*) K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2008, **130**, 14452; (*b*) W. Hu, X. Xu, J. Zhou, W.-J. Liu, H. Huang, J. Hu, L. Yang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2008, **130**, 7782; (*c*) Z.-Y. Han, H. Xiao, X.-H. Chen and L.-Z. Gong, *J. Am. Chem. Soc.*, 2009, **131**, 9182; (*d*) M. Terada and Y. Toda, *J. Am. Chem. Soc.*, 2009, **131**, 6354; (*e*) M. E. Muratore, C. A. Holloway, A. W. Pilling, R. I. Storer, G. Trevitt and D. J. Dixon, *J. Am. Chem. Soc.*, 2009, **131**, 10796; (*f*) B. Xu, S.-F. Zhu, X.-L. Xie, J.-J. Shen and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2011, **50**, 11483; (*g*) J. Jiang, H.-D. Xu, J.-B. Xi, B.-Y. Ren, F.-P. Lv, X. Guo, L.-Q. Jiang, Z.-Y. Zhang and W.-H. Hu, *J. Am. Chem. Soc.*, 2011, **133**, 8428; (*h*) Q.-A. Chen, D.-S. Wang, Y.-G. Zhou, Y. Duan, H.-J. Fan, Y. Yang and Z. Zhang, *J. Am. Chem. Soc.*, 2011, **133**, 6126; (*i*) Q.-A. Chen, M.-W. Chen, C.-B. Yu, L. Shi, D.-S. Wang, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2011, **133**, 16432; (*j*) E. Ascic, J. F. Jensen and T. E. Nielsen, *Angew. Chem., Int. Ed.*, 2011, **50**, 5188; (*k*) E. Ascic, C. L. Hansen, S. T. Le Quement and T. E. Nielsen, *Chem. Commun.*, 2012, **48**, 3345; (*l*) Z.-Y. Han, D.-F. Chen, Y.-Y. Wang, R. Guo, P.-S. Wang, C. Wang and L.-Z. Gong, *J. Am. Chem. Soc.*, 2012, **134**, 6532; (*m*) X.-F. Tu and L.-Z. Gong, *Angew. Chem., Int. Ed.*, 2012, **51**, 11346; (*n*) M. Terada and Y. Toda, *Angew. Chem., Int. Ed.*, 2012, **51**, 2093; (*o*) H. Qiu, M. Li, L.-Q. Jiang, F.-P. Lv, L. Zan, C.-W. Zhai, M. P. Doyle and W.-H. Hu, *Nat. Chem.*, 2012, **4**, 733; (*p*) Q.-A. Chen, K. Gao, Y. Duan, Z.-S. Ye, L. Shi, Y. Yang and Y.-G. Zhou, *J. Am. Chem. Soc.*, 2012, **134**, 2442; (*q*) C. L. Hansen, J. W. Clausen, R. G. Ohm, E. Ascic, S. T. Le Quement, D. Tanner and T. E. Nielsen, *J. Org. Chem.*, 2013, **78**, 12545; (*r*) H. Wu, Y.-P. He and L.-Z. Gong, *Org. Lett.*, 2013, **15**, 460; (*s*) H. Liu, C. Zeng, J. Guo, M. Zhang and S. Yu, *RSC Adv.*, 2013, **3**, 1666; (*t*) V. M. Lombardo, C. D. Thomas and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2013, **52**, 12910; (*u*) A. W. Gregory, P. Jakubec, P. Turner and D. J. Dixon, *Org. Lett.*, 2013, **15**, 4330; (*v*) B. Xu, S.-F. Zhu, X.-D. Zuo, Z.-C. Zhang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2014, **53**, 3913; (*w*) Z.-P. Chen, M.-W. Chen, R.-N. Guo and Y.-G. Zhou, *Org. Lett.*, 2014, **16**, 1406.

3 Pioneering works on chiral phosphoric acid, see: (*a*) D. Uraguchi, K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 11804; (*b*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566. For selected reviews on chiral phosphoric acid, see: (*c*) T. Akiyama, *Chem. Rev.*, 2007, **107**, 5744; (*d*) Y.-J. Gao, L.-H. Yang, S.-J. Song, J.-J. Ma, R.-X. Tang, R.-H. Bian, H.-Y. Liu, Q.-H. Wu and C. Wang, *Chin. J. Org. Chem.*, 2008, **28**, 8; (*e*) Y. Su and F. Shi, *Chin. J. Org. Chem.*, 2010, **30**, 486; (*f*) M. Terada, *Chem. Commun.*, 2008, 4097; (*g*) M. Terada, *Synthesis*, 2010, 1929; (*h*) A. Zamfir, S. Schenker, M. Freund and S. B. Tsogoeva, *Org. Biomol. Chem.*, 2010, **8**, 5262; (*i*) M. Rueping, A. Kuenkel and I. Atodiresei, *Chem. Soc. Rev.*, 2011, **40**, 4539.

4 (*a*) Q. Cai, Z.-A. Zhao and S.-L. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 7428. For other works on sequential catalysis of the cross-metathesis/Friedel–Crafts alkylation reaction see: (*b*) J.-R. Chen, C.-F. Li, X.-L. An, J.-J. Zhang, X.-Y. Zhu and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2008, **47**, 2489; (*c*) X.-L. An, J.-R. Chen, C.-F. Li, F.-G. Zhang, Y.-Q. Zou, Y.-C. Guo and W.-J. Xiao, *Chem. – Asian J.*, 2010, **5**, 2258.

5 For reviews: (*a*) A. Fürstner, *Angew. Chem., Int. Ed.*, 2003, **42**, 3582; (*b*) G. Balme, *Angew. Chem., Int. Ed.*, 2004, **43**, 6238; (*c*) H. Fan, J. Peng, M. T. Hamann and J. F. Hu, *Chem. Rev.*,

2008, **108**, 264; (*d*) S. Thirumalairajan, B. M. Pearce and A. Thompson, *Chem. Commun.*, 2010, **46**, 1797; (*e*) R. Rane, N. Sahu, C. Shah and R. Karpoormath, *Curr. Top. Med. Chem.*, 2014, **14**, 253; (*f*) A. Fürstner, K. Radkowski and H. Peters, *Angew. Chem., Int. Ed.*, 2005, **44**, 2777; (*g*) P. A. Duspara and R. A. Batey, *Angew. Chem., Int. Ed.*, 2013, **52**, 10862.

6 For a book, see: (*a*) *Catalytic Asymmetric Friedel–Crafts Alkylations*, ed. M. Bandini and A. Umani-Ronchi, Wiley-VCH, Weinheim, 2009. For reviews on an asymmetric Friedel–Crafts reaction, see: (*b*) Y. Wang and K.-L. Ding, *Chin. J. Org. Chem.*, 2001, **21**, 763; (*c*) M. Bandini, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 550; (*d*) M. Bandini, A. Melloni, S. Tommasi and A. Umani-Ronchi, *Synlett*, 2005, 1199; (*e*) Y.-F. Sheng, A. J. Zhang, X.-J. Zheng and S.-L. You, *Chin. J. Org. Chem.*, 2008, **28**, 605; (*f*) T. B. Poulsen and K. A. Jørgensen, *Chem. Rev.*, 2008, **108**, 2903; (*g*) S.-L. You, Q. Cai and M. Zeng, *Chem. Soc. Rev.*, 2009, **38**, 2190; (*h*) M. Bandini and A. Eichholzer, *Angew. Chem., Int. Ed.*, 2009, **48**, 9608; (*i*) M. Zeng and S.-L. You, *Synlett*, 2010, 1289; (*j*) V. Terrasson, R. M. de Figueiredo and J. M. Campagne, *Eur. J. Org. Chem.*, 2010, 2635; (*k*) M. Rueping and B. J. Nachtsheim, *Beilstein J. Org. Chem.*, 2010, **6**, 6; (*l*) P. Chauhan and S. S. Chimni, *RSC Adv.*, 2012, **2**, 6117; (*m*) S. Lancianesi, A. Palmieri and M. Petrini, *Chem. Rev.*, 2014, **114**, 7108.

7 For a pioneering asymmetric Friedel–Crafts alkylation of pyrrole, see: (*a*) N. A. Paras and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2001, **123**, 4370. Selected latest examples, see: (*b*) Y.-F. Sheng, Q. Gu, A.-J. Zhang and S.-L. You, *J. Org. Chem.*, 2009, **74**, 6899; (*c*) P. K. Singh and V. K. Singh, *Org. Lett.*, 2010, **12**, 80; (*d*) W. Kashikura, J. Itoh, K. Mori and T. Akiyama, *Chem. – Asian J.*, 2010, **5**, 470; (*e*) F. Guo, D. Chang, G. Lai, T. Zhu, S. Xiong, S. Wang and Z. Wang, *Chem. – Eur. J.*, 2011, **17**, 11127; (*f*) K. Aikawa, K. Honda, S. Mimura and K. Mikami, *Tetrahedron Lett.*, 2011, **52**, 6682; (*g*) L. Liu, H. Ma, Y. Xiao, F. Du, Z. Qin, N. Li and B. Fu, *Chem. Commun.*, 2012, **48**, 9281; (*h*) M. Zeng, W. Zhang and S.-L. You, *Chin. J. Chem.*, 2012, **30**, 2615; (*i*) D. Hack and D. Enders, *Synthesis*, 2013, 2904; (*j*) D. Zhang, H. Qiu, L. Jiang, F. Lv, C. Ma and W. Hu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13356; (*k*) Y.-Z. Hua, X.-W. Han, X.-C. Yang, X. Song, M.-C. Wang and J.-B. Chang, *J. Org. Chem.*, 2014, **79**, 11690.

8 (*a*) Q. Cai, C. Zheng and S.-L. You, *Angew. Chem., Int. Ed.*, 2010, **49**, 8666; (*b*) Q. Cai, X.-W. Liang, S.-G. Wang, J.-W. Zhang, X. Zhang and S.-L. You, *Org. Lett.*, 2012, **14**, 5022; (*c*) J.-W. Zhang, Z. Xu, Q. Gu, X.-X. Shi, X.-B. Leng and S.-L. You, *Tetrahedron*, 2012, **68**, 5263; (*d*) Q. Cai, X.-W. Liang, S.-G. Wang and S.-L. You, *Org. Biomol. Chem.*, 2013, **11**, 1602; (*e*) J.-W. Zhang, Q. Cai, Q. Gu, X.-X. Shi and S.-L. You, *Chem. Commun.*, 2013, **49**, 7750; (*f*) Y.-C. Shi, S.-G. Wang, Q. Yin and S.-L. You, *Org. Chem. Front.*, 2014, **1**, 39.

9 J. C. Conrad, J. Kong, B. N. Laforteza and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2009, **131**, 11640.